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Lipid-like trifunctional block copolymers of ethylene oxide and propylene oxide: Effective and cytocompatible modulators of intracellular drug delivery

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ABSTRACT

A new glycerol-based trifunctional block copolymer (TBC) of propylene oxide and ethylene oxide a its conjugate with succinic acid (TBC–SA) were studied as a drug delivery system and compared w Pluronic L61. TBCs have multiple effects on the plasma membrane of human cells, e.g. increasing fluidity and ion permeability, inhibiting ATPase activity of efflux transporter P-glycoprotein throu reversible membrane destabilization. Such membrane-modulating properties attributed to the unim form of copolymers increase in the order Pluronic L61 ≪ TBC < TBC–SA and correlate with an ability TBCs to promote the accumulation of P-glycoprotein substrates in lung cancer A549 cells. Furthermo TBC, and especially TBC–SA, exhibit substantially lower hemolytic, cytotoxic and proapoptotic activit in comparison with Pluronic L61. Our results demonstrate that TBCs are promising analogs of bifunctio Pluronics in anticancer drug delivery.

1. Introduction

Nonionogenic amphiphilic polymers have a variety of applications in petroleum production, chemical technologies and are also an important component of household products. Depending on their physicochemical properties, e.g. the hydrophilic–lipophilic balance (HLB), such polymers exhibit different effects on living cells as a result of a reversible interaction with amphiphilic cellular components, especially lipid membranes and membrane-associated proteins (Firestone and Seifert, 2005; Batrakova and Kabanov, 2008; Alakhova et al., 2010). The biological properties of these amphiphilic polymers are of particular interest with regard to their potential (cyto-)toxicity, as well as an intriguing possibility of their therapeutic application.

Bifunctional block copolymers of ethylene oxide and propylene oxide (Pluronics™) have been systematically studied as drug carriers (Venne et al., 1996; Kabanov et al., 2002; Batrakova and Kabanov, 2008; Valle et al., 2011; Wei et al., 2013). Pluronic-based micellar formulations allow for the encapsulation of hydrophobic drugs, improving their solubility and increasing blood circulation time (Wang et al., 2007; Yoncheva et al., 2012). Other applications of Pluronics include the development of: hydrogels for topical drug delivery (Jansen et al., 2013), immuno-adjuvants (Newman et al., 1998) and cellular membrane protectors (Serbest et al., 2006; Mi et al., 2009).

Although in above applications Pluronics have been exploit as relatively inert surfactants, a series of recent studies show th Pluronics may directionally affect some cellular functions inclu ing: gene expression (Batrakova and Kabanov, 2008), energe metabolism (Alakhova et al., 2010) and membrane transpor activity (Wei et al., 2013). These effects are more pronounced Pluronics with low and intermediate HLB, such as Pluronics L and P85, which were found to promote drug transport across t blood brain barrier as well as into multidrug resistant cancer ce making them more sensitive to conventional chemotherapy (Ven et al., 1996; Batrakova and Kabanov, 2008). To date, several co positions of existing anticancer drugs and Pluronics L61/F127 ha been developed by Supratek Pharma Inc. to treat solid tumors a leukemia. One formulation SP1049C containing the anthracycli antibiotic doxorubicin is in phase III of clinical trials (Valle et 2011).

The principal limitation of hydrophobic Pluronics (e.g. Pluro L61) as candidates for drug delivery is high cytotoxic/proapopto action which restricts their pharmaceutical application. Sa amphiphilic polymers with balanced specific and cytotoxic act ities are ones of choice in advanced polymer-based therapy. promising strategy is the development of polyfunctional analo of Pluronics on the basis of biochemical structures. Recently, have demonstrated that the conjugation of hydrophobic Pluro ics with succinic acid modulates their interaction with the plas

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